

## REVIEW

# The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 4: Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research

Konstantinos N. Fountoulakis, MD; Eduard Vieta, MD; Allan Young, MD; Lakshmi Yatham, MD; Heinz Grunze, MD; Pierre Blier, MD; Hans Jurgen Moeller, MD; Siegfried Kasper, MD

Associate professor of Psychiatry, 3rd Department of Psychiatry, School of Medicine Aristotle University of Thessaloniki Greece (Dr Fountoulakis); Professor, Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain (Dr Vieta); Professor, Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, United Kingdom (Dr Young); Department of Psychiatry, University of British Columbia, Mood Disorders Centre of Excellence, Djavad Mowafaghian Centre for Brain Health, Vancouver, Canada (Dr Yatham); Paracelsus Medical University, Salzburg, Austria (Dr Grunze); The Royal Institute of Mental Health Research, Department of Psychiatry, University of Ottawa, Ottawa, Canada (Dr Blier); Psychiatric Department Ludwig Maximilians University, Munich, Germany (Dr Moeller); Department of Psychiatry and Psychotherapy, Medical University Vienna, Vienna, Austria (Dr Kasper).

Correspondence: Konstantinos N. Fountoulakis, MD, 6 Odysseos str (1st Parodos Ampelonon str.), 55535 Pylaia, Thessaloniki, Greece ([kfount@med.auth.gr](mailto:kfount@med.auth.gr)).

## Abstract

**Background:** The current fourth paper on the International College of Neuropsychopharmacology guidelines for the treatment of bipolar disorder reports on the unmet needs that became apparent after an extensive review of the literature and also serves as a conclusion to the project of the International College of Neuropsychopharmacology workgroup.

**Materials and Methods:** The systematic review of the literature that was performed to develop the International College of Neuropsychopharmacology guidelines for bipolar disorder identified and classified a number of potential shortcomings.

**Results:** Problems identified concerned the reliability and validity of the diagnosis of bipolar disorder and especially of bipolar depression. This, in turn, has profound consequences for early detection and correct treatment of the disorder. Another area that needs improvement is the unsatisfactory efficacy and effectiveness of therapeutic options, especially in special populations such as those with mixed features and rapid cycling course. Gender issues and adherence problems constitute an additional challenge. The literature suggests that while treatment providers are concerned more with treatment-related issues, patients and their caregivers worry more about issues pertaining to the availability of services and care, quality of life,

Received: July 1, 2016; Accepted: August 9, 2016

© The Author 2016. Published by Oxford University Press on behalf of CINP.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

and various types of burden. The workgroup identified additional unmet needs related to the current standard of research in bipolar disorder. These include the fragmentation of bipolar disorder into phases that are handled as being almost absolutely independent from each other, and thus the development of an overall therapeutic strategy on the basis of the existing evidence is very difficult. Trials are not always designed in a way that outcomes cover the most important aspects of bipolar disorder, and often the reporting of the results is biased and unsatisfactory. The data on combination treatments and high dosages are sparse, whereas they are common in real world practice.

**Conclusions:** The workgroup endorses the full release of raw study data to the scientific community, and the development of uniform clinical trial standards (also including more realistic outcomes) and the reporting of results. The 2 large appendices summarize the results of this systematic review with regard to the areas of lack of knowledge where further focused research is necessary.

**Keywords:** BD, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment

## Background

The first 3 papers of the International College of Neuropsychopharmacology (CINP) guidelines for the treatment of bipolar disorder (BD) consisted of a systematic and exhausting review of the literature concerning the available hard data on treatment options and a description of the major clinical challenges the therapist faces together with the patient and his/her family.

The workgroup developed a precise experimental algorithm and a clinical guideline for the treatment of BD, but it is obvious that these products are far from perfect. In fact there are a significant number of issues and needs that were not addressed due to a lack of evidence-based data. Suboptimal treatment and management, however, puts the patients at a higher risk for an adverse outcome with more residual symptoms and higher disability.

This is of utmost importance, since BD is a rather common and complex mental disorder accompanied by significant morbidity and mortality, including a high rate of suicide, while it is obvious that the treatment needs are not fully met by currently available pharmacotherapies and psychosocial interventions of any kind. The problem is further complicated by the poor adherence to treatment that many patients show and the somatic comorbidities that in some cases are adverse effects of medication.

The current paper is the fourth and last of the initiative to develop CINP guidelines for the treatment of BD and summarizes the experience gained from the whole project. It identifies the unmet needs and makes suggestions for future research and the way of dealing with specific issues in BD.

## 1. Unmet Needs Identified in the Literature (Summarized in Tables 1 and 2)

### Diagnosis

The first and maybe biggest problem in the management of BD is the difficulty in making early correct diagnosis (Lish et al., 1994; Lewis, 2000; Hirschfeld et al., 2003; Morselli et al., 2003). In a majority of patients the first episode is depressive, and thus they receive the diagnosis of unipolar depression and they are mistreated with antidepressant monotherapy (Vieta, 2014). It has been reported that as many as 70% of BD patients failed to receive a correct diagnosis in the 1-year period following the initial episode, and in approximately 35% of them the correct diagnosis has been made only after 10 years had passed (Lish et al., 1994). Additionally, up to 70% of BD patients but especially bipolar spectrum patients often go unrecognized and undiagnosed, and thus remain untreated or

inappropriately treated (Hirschfeld et al., 2003; Frye et al., 2004; Ketter, 2010). Since BD patients are most often misdiagnosed as suffering from unipolar depression or some type of personality disorder, they are frequently treated with antidepressants only or an inappropriate type of psychotherapy for prolonged periods of time.

This problem may persist until the day psychiatric diagnosis is not exclusively based on clinical phenotypes but on reliable and valid biological markers that can be utilized for precise diagnostic differentiation and treatment planning. Of all mental disorders, BD is the one that will probably benefit the most from the introduction of reliable and valid biological markers to our diagnostic armamentarium.

Additionally, physical health problems, especially in bipolar spectrum patients, are underrecognized and undertreated (Merikangas et al., 2011). This is probably a consequence of stigma but also of an unhealthy lifestyle, poor treatment adherence, and only irregular contacts with health care services.

### Efficacy and Effectiveness of Therapeutic Options

All authors agree that only 2 to 3 agents have some efficacy across all phases, and no single pharmacotherapy is currently achieving remission in a satisfactory proportion of BD patients both across all phases and in the long term. Acute episodes comprise a relatively small time share of the overall illness, but subthreshold or subclinical symptoms dominate the clinical picture for most of the duration of the lives of patients, causing significant impairment, disability, and burden (Judd et al., 2002, 2003; Morgan et al., 2005). Since no single pharmacologic treatment is likely to achieve all therapeutic objectives, combining treatments is usually necessary to achieve an acceptable quality of life (Grande et al., 2016).

The very concept of what constitutes a “mood stabilizer” is under dispute, since there is no agent that is efficacious against all phases and all major clinical features of BD (manic, mixed, and depressive episodes, rapid cycling). Historically, lithium, valproate, and carbamazepine have all been considered to act as mood stabilizers, but today we have to acknowledge that some atypical antipsychotics, namely quetiapine and olanzapine, do also fulfil many criteria of a mood stabilizer. When it comes to clinical usefulness, while antipsychotics may act faster in acute mania and are also definitely efficacious against psychotic features, there are concerns with the safety profile of all agents useful in the treatment of BD, such as metabolic syndrome with antipsychotics, kidney and thyroid issues with lithium.

Almost all the literature concerning the treatment of all phases of BD focuses on reporting changes from baseline in a symptom rating scale and neglects other important aspects, including disability, quality of life, burden, and economic issues. Most researchers agree that currently available treatments are more efficacious in the reduction of symptoms than in the improvement of disability and the overall outcome (Bauer et al., 2001a; Calabrese et al., 2014; Frye et al., 2014; McElroy, 2014). This is especially true concerning bipolar depression, which is a rather refractory mental state with high risk for suicide (Akiskal et al., 1983; Weissman et al., 1984; Frye et al., 2004, 2014) and profound and lasting functional impairment (Bonnin et al., 2015). Residual symptoms may interfere with the ability of the patients to access and benefit from health care but also from the general state welfare (Gerson and Rose, 2012). Particularly in those patients with more severe disability, functional decline, and poor quality of life, the overall burden is further increased by a higher mortality from comorbid medical conditions (McIntyre et al., 2007) and suicide (Morgan et al., 2005). In these cases, the burden is also higher for caregivers, and the increased service utilization leads to a higher overall cost. This is made even worse when discriminatory coverage and reimbursement policies for mental health care are in place as they are in many countries around the world (Charney et al., 2003; Morgan et al., 2005).

It is unfortunate (although the reasons are apparent) that, by far, fewer randomized controlled trials (RCTs) have been conducted on the treatment of acute bipolar depression than for acute mania (Han et al., 2013). The changing composition of the study samples is a developing problem for all RCTs in mental disorders, and it seems that nowadays larger numbers of patients are required to demonstrate a significant effect compared with earlier studies, although the reasons for this are not entirely understood (Sachs, 2003).

Comprehensive managed care comprising of intensive follow-up, psychosocial and psychological treatment, and functional rehabilitation is not easily accessible to patients, even in developed countries. Lack of access to such services probably adversely influences the overall long-term outcome (Morgan et al., 2005; Goossens et al., 2007).

## Gender

While it is known that there are gender-specific factors that can influence the treatment and overall management of patients with BD (Leibenluft, 1996; Hendrick et al., 2000; Leibenluft, 2000; Curtis, 2005), little research has been conducted in this area. This is important since unmet needs could differ between males and females (Curtis, 2005; Morgan et al., 2005).

Although the prevalence of BD-I is similar between genders (Morgan et al., 2005), more females suffer from BD-II (Leibenluft, 1996) and depressive predominant polarity (Nivoli et al., 2011). In addition, rapid cycling, mixed episodes, and dysphoric mania but also hypothyroidism and personality disorders might be more prevalent in females (McElroy et al., 1992; Arnold et al., 2000; Judd et al., 2002; Post et al., 2003; Morgan et al., 2005), while suicidality, psychotic features, and hospitalizations are more frequently seen in males (Morgan et al., 2005). There is a greater incidence of a childhood history of sexual abuse among female patients (Hyun et al., 2000), and this is probably true also for adulthood (Coverdale and Turbott, 2000). A history of sexual abuse or the high risk to become a victim might justify nursing the patient in a single-sex environment, although such environments are vanishing. There are some data suggesting a different risk depending on gender comorbid alcohol and substance

abuse (Hendrick et al., 2000; Frye et al., 2003). As protective factors, female patients with BD less often stay single or are without children and less frequently live alone. They seem to maintain better global functioning compared with male patients with BD (Morgan et al., 2005).

The most prominent issues with female BD patients are around the reproductive cycle and related physiology. While the influence of the menstrual cycle and menopause on the course of BD is still unclear, there are some research data on the effects of motherhood. It is simply reasonable that in the case of a pregnant patient, multidisciplinary care together with the obstetrician and midwife is mandatory.

The most commonly emerging issues concern unwanted pregnancy (Coverdale et al., 1997). Therefore, bipolar women of childbearing age should receive intense counseling regarding effective contraceptive practice, issues pertaining to interaction of contraceptive pills with medication for BD, and the possible effects of pregnancy and delivery on the course of bipolar illness. Also the treatment options during pregnancy and breast feeding should be discussed along with the psychological and somatic stress of pregnancy and child-rearing, and the effects treatment might have on the fetus depending on the trimester of gestation. Finally, counselling about the genetic risk of BD should be offered also to siblings to enable informed decisions for future pregnancies (Packer, 1992; Cohen et al., 1994). In everyday practice, few patients consider the risks related to pregnancy unacceptable, and these should be guided to use effective contraception, which should be considered together with the medication the patient receives to treat BD. Several drugs, for example carbamazepine, oxcarbazepine, lamotrigine, and topiramate, all increase the clearance rate of oral contraceptives, and thus the doses of oral contraceptive for patients taking these medications need to be adjusted and/or other protective strategies need to be implemented as a standard of care.

According to some studies, pregnancy is associated with a reduced overall risk for psychiatric admission (Kendell et al., 1987) and a lower risk for suicide (Appleby, 1991; Marzuk et al., 1997) and may improve the clinical course of BD (Sharma and Persad, 1995; Grof et al., 2000), but there are also reports of the opposite (Blehar et al., 1998; Freeman et al., 2002). On the other hand, there is a broad consensus that the postpartum period confers the greatest risk for exacerbation of BD (usually within 90 days) (Dunner et al., 1979; Brockington et al., 1981; Davidson and Robertson, 1985; Kendell et al., 1987; Schopf and Rust, 1994; Leibenluft, 1996; Blehar et al., 1998; Freeman et al., 2002).

Besides the issues concerning the reproductive cycle, female patients appear to be at greater risk for a number of medication adverse effects, including weight gain (Fakhoury et al., 2001; Russell and Mackell, 2001) and extreme obesity (McElroy et al., 2002) and decrease in bone mineral density as a result of prolonged hyperprolactinemia (Wieck and Haddad, 2003), which could also cause a hypogonadal state (Smith et al., 2002).

## The Therapists' Point of View

There is not much data concerning the point of view of psychiatrists and of therapists in general on the unmet needs in the treatment of BD patients.

One study reported that psychiatrists in the UK and US consider education and support for patients and families as well as earlier referral to specialist care as the highest ranked needs at entry into care. On the other hand, they thought that during treatment of acute episodes and also during the long-term

**Table 1.** Unmet Needs in the Treatment of BD Patients Identified in the Literature

---

Diagnosis char="12"
<ul style="list-style-type: none"> <li>• Early correct diagnosis</li> <li>• Recognition and treatment of somatic health problems</li> </ul>
Efficacy and effectiveness of therapeutic options
<ul style="list-style-type: none"> <li>• Only 2–3 agents are efficacious across all phases</li> <li>• The definition of 'mood stabilizer' is problematic</li> <li>• Combining treatments is usually necessary to achieve an acceptable level of efficacy</li> <li>• Research so far neglects outcomes like disability, quality of life, burden, and economic issues</li> <li>• Limited data on treatments for acute bipolar depression</li> <li>• Lack of access to specialized care services</li> </ul>
Gender
<ul style="list-style-type: none"> <li>• Little research on gender issues</li> <li>• There are some data suggesting that gender is related to different clinical pictures, adverse events profile and to different outcomes</li> <li>• Issues related to female physiology and reproduction, especially pregnancy and breast feeding</li> </ul>
Unmet needs: the therapists' point of view
<ul style="list-style-type: none"> <li>• Education and support for patients and families</li> <li>• Earlier referral to specialist care</li> <li>• Improved effectiveness and patient adherence</li> <li>• A minority of therapists adheres to evidence-based standards</li> <li>• There is an unmet need for the continuous education of professionals</li> </ul>
Unmet needs: the patients' and caregivers' point of view
<ul style="list-style-type: none"> <li>• Clinical research never focuses on the unmet needs as the patients conceive them</li> <li>• The generalizability of research data to the real-world patient is unknown</li> <li>• Burden of caregivers of patients</li> </ul>
Adherence to treatment
<ul style="list-style-type: none"> <li>• Psychoeducation is not routinely applied at the earlier stages</li> <li>• Empowerment of service users is not the standard</li> </ul>

---

management, the most important needs were improved effectiveness of treatments and patient adherence in addition to improved long-term safety in the maintenance phase. These mental health professionals ranked patients with comorbid alcohol and/or substance use disorders as having the highest level of unmet need, followed by rapid-cycling patients (Chengappa and Williams, 2005).

A second study reported that clinicians were not adherent to evidence-based practice and that their clinical practice was not consistent with the results of clinical trial data or current guideline recommendations. Additionally, there seems to be an unmet need for education to enable psychiatrists to differentiate between unipolar and bipolar depression, to identify the risk of treatment-emergent mood disorders with the use of antidepressants, and to effectively manage patients at risk for BD-I. It is surprising that only one-half of the respondents thought that treatment guidelines should be important in their everyday clinical practice, and additionally they also reported that clinical trial results were the least influential. Furthermore, only one-third of the respondents were familiar with large practical clinical trials and scientific associations, organizations, and other bodies relating to BD (Glauser et al., 2013). Overall, the findings clearly indicate that many clinicians are not well informed about the evidence base of their treatment choices for BD patients, especially for depressive symptoms, and they are also not well trained concerning the clinical assessment and management of BD (Han et al., 2013). Guidelines to provide comprehensive introductory information, suggestions, and resources for caregivers

**Table 2.** Unmet Needs in the Treatment of BD Patients As Identified During the Process of Guideline Development

---

Fragmentation of BD as a disorder char="12"
<ul style="list-style-type: none"> <li>• Research does not consider BD as a single disorder but as a sequence of largely independent phases</li> <li>• Almost impossible to reliably transform the available data into a longitudinal treatment strategy</li> </ul>
Unsatisfactory design of RCTs
<ul style="list-style-type: none"> <li>• Scales do not cover the full symptomatology of BD</li> <li>• Recognition and reporting of diagnostic criteria and specifiers is problematic</li> <li>• Duration too short for acute mania and acute bipolar depression studies</li> <li>• Duration of the continuation phase too short before entering the maintenance phase</li> <li>• Use of enriched samples almost in all maintenance studies</li> <li>• Research on substance and alcohol abuse and medical comorbidities is insufficient</li> </ul>
Focus on more realistic outcomes
<ul style="list-style-type: none"> <li>• General impairment and disability</li> <li>• Neurocognitive function</li> <li>• Social and occupational functioning</li> <li>• Quality of life</li> </ul>
Limited data concerning combination treatment and high dosages
Incomplete results reporting
<ul style="list-style-type: none"> <li>• Core symptoms of mania or depression</li> <li>• Mixed features</li> <li>• Data exist mostly on the manic but not the depressive component of mixed episodes</li> <li>• Psychotic symptoms</li> <li>• Rapid cycling</li> <li>• Incomplete descriptive statistics</li> </ul>
Reporting of the results
<ul style="list-style-type: none"> <li>• Inconsistent way of reporting</li> <li>• Often different study samples sizes are reported in different documents concerning the same study</li> <li>• Last Observation Carried Forward vs Mixed-Effect Model Repeated Measure</li> </ul>

---

**Table 3.** Recommendations of the Workgroup for Further Research

---

Availability of the raw data char="12"
Study design
<ul style="list-style-type: none"> <li>• Study any acute mood episode with the same broad protocol</li> <li>• Anxiety and psychotic symptoms should also be assessed</li> <li>• Assessment of neurocognitive function in long-term studies</li> <li>• Assessment of disability and social and occupational functioning and quality of life</li> <li>• Adequate duration of studies</li> <li>• Separate studies of both enriched and nonenriched samples in maintenance studies</li> <li>• Studies focusing on mixed depression</li> </ul>
Proposed template for a standardized reporting of the results (see appendix)

---

have been developed to assist them to formulate treatment strategies ranging from a stepped-care approach to supporting caregivers, ranging from basic information and pamphlets to brief training courses and specialized family or caregiver interventions based on need and accessibility (Berk et al., 2011).

### The Patients' and Caregivers' Point of View

It is well known that different "stakeholders" emphasize different unmet needs, and therefore the point of view of patients and caregivers might vary considerably from the point of view



of mental health professionals (Chengappa and Goodwin, 2005). What may contribute to poor adherence is the fact that clinical research hardly focuses on the unmet needs as the patients perceive them and therefore, at least to some extent, real world needs are not addressed (Bauer, 2002). Even more, it is not known to what extent clinical trials data apply to those patients who are not eligible to be included in standardized controlled research, because they suffer from multiple comorbidities or have shown refractoriness to treatment in the past (Wells, 1999; Bauer et al., 2001b; Simon et al., 2002; Wells et al., 2002; Sachs et al., 2003; Bauer and Mitchner, 2004). There is also profound discrepancy between the interpretation by mental health professionals of the evidence base for treatments in BD and patient perception of the relative effectiveness of different treatment options (Masand and Tracy, 2014).

If the real outcome of mental disease is what patients report concerning their quality of life, research gives a grim picture with patients with severe mental illness reporting dissatisfaction with their social functioning and general health and unmet needs concerning case management services, social and recreational activities, and vocational rehabilitation (Badger et al., 2003).

Caregivers of patients with BD may experience a different quality of burden than is seen with other illnesses, and it is definitely more severe compared with the burden of caregivers of patients with unipolar depression. However, there is not enough research data on this issue, which is largely neglected (Reinares et al., 2006). Conceptualizing the burden of a bipolar caregiver in a conventional medical framework may not focus enough on important issues or on cultural and social issues as well as on the objective and subjective aspects of burden. An important fact is that burden to caregivers is associated with caregiver depression, which conversely affects patient recovery by adding stress to the home environment. It is also associated with high levels of expressed emotion, including critical, hostile, or over-involved attitudes. It is reasonable to assume that it is not possible to ameliorate service provision without a better understanding of caregiver burden and the means to measure and target it (Ogilvie et al., 2005).

## Adherence to Treatment

Poor treatment adherence is a major problem in mental health care, and especially in BD it is associated with poor outcome (Keck et al., 1996; Bauer et al., 2001a). Depending on definition and setting, it has been reported that between one- and two-thirds of BD patients are noncompliant with treatment (Johnson and McFarland, 1996; Keck et al., 1996; Murru et al., 2013). Adverse events are one of the reasons patients are often unwilling to continue medication treatment for prolonged periods of time. Some might also wish to continue to have the experience of manic or especially of hypomanic episodes, which are particularly pleasant. Psychoeducation and collaborating with patients and caregivers enables patients to be active participants in the management process, and this is believed to improve treatment adherence (Sachs, 2013). It is interesting to note that both patients and their families often seemed to lack a thorough understanding of disease management goals and the need for follow-up care (Lish et al., 1994).

Therefore, there seems to be a clear need for more empowerment of patients and their caregivers. Currently they appear less than optimally informed concerning the need and benefits of continuation treatment and care, with the result of high rates of poor treatment adherence.

## 2. Unmet Needs Identified by the CINP Guidelines Project

As described and reported in the previous papers of the CINP guidelines, the workgroup synthesized and analyzed the accessible data on the efficacy of existing treatment options for BD. The essential result was a large table of efficacy data for each treatment option across different phases of the illness and considering specific clinical features. The analysis, classification, and tabulation of the results revealed a number of important problems and unmet needs as well as areas that should be the focus of research in the future.

### Fragmentation of BD As a Disorder

A major problem of the literature is that it is almost impossible to reliably assemble the available data in a longitudinal treatment strategy that would take into consideration the present phase but also the psychiatric history and possible future development. That is, the data do not consider BD as a single disorder but as separate and literally independent phases. At the guidelines but also the clinical level, it creates a very important dilemma. What should the decision for the maintenance treatment be in case the patient was treated (and responded to) with a treatment with no data concerning the long-term prophylactic treatment, or even worse with negative data concerning the assumed possible future of his or her mental health? For example, a patient has responded favorably to haloperidol during an acute manic episode, but since the patient's history indicates that the overwhelming majority of the mood episodes were depressive episodes (depressive predominant polarity), it is fair to assume that these episodes will continue to be frequent. In such a case, the therapist is left with a dilemma: should he or she add an agent with proven preventive efficacy against depressive episodes, for example quetiapine, and apply combination treatment, or should he or she change to monotherapy with an agent with proven prophylactic efficacy against both poles? The answer is not apparent and different opinions do exist, especially since almost all maintenance studies include enriched samples, that is samples of patients who responded during the acute phase specifically to the agent under research. Especially in cases of partial or poor response to first line treatment, it is unknown which would be the best next option. Switching might prolong suffering while adjunctive treatment will result in polypharmacy.

Future research should focus on these problems and provide specific answers. Ideally, all treatment options should be tested against all phases and clinical features of BD, and those with broader efficacy should receive priority in the use. Of course safety and tolerability issues might additionally perplex the problem.

### Unsatisfactory Design of RCTs

The inclusion of too many scales probably creates severe problems with the completion of RCTs; however, the trials should include those scales that have been proven to be of high importance for everyday clinical practice. In addition, reporting should not only include global measures but inform professionals more specifically which diagnostic features and specifiers of BD responded to a given treatment. However, the total costs of a trial and the feasibility need to be balanced against the research benefits.

In this framework, the design of future clinical trials should take into consideration that outcomes should address issues

like mixed features, anxiety, psychotic symptoms, neurocognitive disorder, and disability. Currently there are few data on mixed features in acute bipolar depression, and almost all data on mixed episodes come from acute mania trials. At the same time, the overall design should keep the effort for the patients and the researchers at a minimum by avoiding unnecessary ratings and making RCTs feasible.

An important concern to mention is the duration of the continuation phase before entering the maintenance phase, which is often unacceptably short. This is sometimes the case for acute phase studies and especially for bipolar depression. Since the aripiprazole studies had positive results at week 6 but negative at endpoint, which was week 8 (Thase et al., 2008), it is reasonable to suggest that the minimum duration for acute bipolar depression studies should be 8 weeks to capture true and lasting improvement. However, this is not always the case, and at least one agent gained approval with a positive study of only 6 weeks duration (Loebel et al., 2014).

While the enriched designs inform about the longer term efficacy of an agent if it was effective for an acute phase, they do not provide information about whether or not they have broader spectrum of prophylactic efficacy (i.e., prophylactic efficacy in patients who responded to other agents during acute phase). While many agents that are effective in acute phase appear to provide benefit during the maintenance phase, it is unknown whether this can be generalized to all agents for the maintenance period.

In acute mania, a study duration of 3 weeks appears not adequate; however, most studies utilized this short duration. Probably the best solution would be to utilize a 12-week design both in acute mania and depression RCTs that may allow for assessing both manic and depressive symptoms that often coexist. The use of placebo is acceptable, but ideally a third arm with a comparator would be more informative for assay sensitivity (Vieta and Cruz, 2012).

Research on substance and alcohol abuse and medical comorbidities should be a specific target of research and probably cannot be incorporated in the frame of the standard RCTs. Large observational studies may be needed to supplement controlled trials.

### Focus on More Realistic Outcomes

Almost all the RCTs are industry sponsored, and therefore their primary aim is to obtain labelling for the product. Thus, the primary outcome is always the change in the total score of a scale that measures the symptoms of the acute phase (YMRS, MRS, MADRS, or the HAM-D), while the CGI or the PANSS are included as secondary outcomes. Rates of response and remission are almost always included as secondary outcomes. Relapse into a mood episode is the most usual primary outcome for maintenance studies.

It is very rare that measurements of general impairment, neurocognitive function, social and occupational quality of life, etc. are utilized. Although the currently used outcomes serve the purpose to test whether the agent under consideration is efficacious or not, they fail to capture aspects of treatment that are equally clinically relevant and of high importance for the everyday clinical practice.

### Limited Data Concerning Combination Treatment and High Dosages

While in everyday clinical practice polypharmacy is the rule rather than the exception, the research data in support of most combination options are weak or absent. This is also the case with the use of high dosages, which is often everyday clinical practice.

### Incomplete Results Reporting

Although the data are often available, the authors and the manufacturers decide not to report them. Examples include the effect of treatment options on the core symptoms of mania or depression and on mixed features, psychotic symptoms, rapid cycling, etc. Often only P values are reported without means and SDs and at other times the opposite happens, thus adding confusion. In many instances, total scale scores with problematic interpretation (e.g., total PANSS score) are reported without a more detailed subanalysis. Sometimes the data are not available for the entire study sample and thus different sample sizes apply for each outcome; however, this is not always made transparent. It is unacceptable that usually in mixed episodes only the effect of the treatment modality on the manic component is reported but the effect on the depressive component is missing.

It is desirable for the raw data to be released and accessible for the scientific community. Much advancement in our knowledge and ability to treat BD patients better may arise not from new and expensive research but from simply exhaustively analyzing existing data. The release of the raw data will also remove publication bias and improve the reliability of conclusions.

### Reporting of the Results

The overall impression from the review of the literature is that the results are reported in a nonhomogenous way and although some kind of a template exists, it is not always possible to detect and extract all details. This is a particular problem when extracting data to perform meta-analysis. Important details are often missing, for example, the score on the positive subscale of the PANSS, while others that are less important exist, for example, the PANSS total score. In most instances, a Last Observation Carried Forward approach is utilized while in a minority the Mixed-Effect Model Repeated Measure is used. In some cases the results are reported selectively from either model. Each model/approach has its advantages and disadvantages (Siddiqui et al., 2009). It is also dubious that often different numbers for study samples are found in different publications of the same original study. It is also important that reports fulfil the CONSORT requirements.

## 3. Recommendations for Future Research Policies (Summarized in Table 3)

### Availability of the Raw Data

The wealth of data that has been accumulated but not exhaustively analyzed is huge. The full release of these data will not only provide us with answers to a number of questions but it will also eliminate much of the publication bias that makes conclusions difficult. One of the most important questions that, if not answered, then at least could lead to a much better understanding is which (if any) baseline clinical characteristics predict response to specific treatments.

Since for the vast majority of treatment options the patents have expired, there is no practical reason for the industry to justify the withholding of the data except of a possible loss of face if a previously biased reporting becomes apparent. However, even in the case of those agents still under patent, the benefit for the public health should be considered as more important than any supposed commercial interest. In any case, this should be considered to be a matter of transparency.

## Study Design

Future RCTs conducted for licensing purposes will probably need to consider any acute mood episode in a similar way. Since pure episodes of either pole are not the rule but rather the exception and with the “mixed features” specifier in place by the DSM-5, it is important to assess the presence of depressive symptoms in acute mania and manic symptoms in acute bipolar depression. In either case, anxiety and psychotic symptoms should also be assessed. This means that in all RCTs, YMRS or MRS, MADRS or HAM-D, HAM-A, and PANSS need to be included. It is desirable although difficult to include regular assessments of neurocognitive function especially in maintenance studies. For long-term studies, the assessment of disability and especially of social and occupational functioning and quality of life should be mandatory.

## Template for a Standardized Reporting of the Results

As already mentioned, there is a need to standardize the reporting of RCT results and make sure that not only all important results are released but also in a manner that adds to our understanding of the treatment of BD and also makes further analysis possible. Such standardization will also increase the reliability of the reports and eliminate the reporting of slightly different results in different articles concerning the same study. A proposed template for the reporting of RCT results is shown in the appendix. The template is laid out for 2 arms (agent vs placebo), and in cases of different design (no placebo or 3-arm design) it should be modified accordingly. It is suggested that both the results according to Last Observation Carried Forward and Mixed-Effect Model Repeated Measure should be reported. Also it seems important to have a standardized list of adverse events and procedure how to capture them, so that it will be easy to compare across studies. The template presented in the appendix is a convenient summary that can be used as a guide as to which results could be of importance and should be reported.

## 4. Discussion

It is clear that unmet clinical needs exist for all phases of BD. While the review of the literature suggests that early and reliable diagnosis as well as gaps in the education of patients and their families could constitute the biggest unmet needs in the area of BD, the experience from the analysis of the existing evidence identified additional important problems concerning the available knowledge and the way research is carried out.

One important conclusion is that the existing data may already provide answers to a number of clinical questions, including the specific treatment of subgroups of patients. However, relevant analyses have not been carried out and the raw data are not released. Taking full advantage of the data already gathered might have an impact that will have a greater impact in the short term than any new research. There is a pressing need and it is for the benefit of public health that the data should be released and such analyses are carried out.

On the other hand, it is also evident that a standardized design for future RCTs is desirable that reflects the complex clinical picture of BD, with the simultaneous rating of manic, depressive, and psychotic symptoms during all phases of the disorder. The design should be standardized to avoid biases and uncertainties that are frequent because of the current way things are carried out.

A standardized way of reporting the results also seems necessary, since currently only a small and often patchy part of the results is available. It is not unusual that different documents that all report the results of the same trial include slightly different figures. This raises the issue of overall reliability on the current mode of scientific reporting. Besides reporting and appraising the evidence, guidelines should also be educational and promote good practice. The authors hope that the CINP guidelines on BD will have a positive impact on the methodology of future patient-orientated research.

## Supplementary Material

For supplementary material accompanying this paper, visit <http://www.ijnp.oxfordjournals.org/>

## Acknowledgment

The authors thank Professor Guy Goodwin for his valuable input in the authoring of this manuscript.

## Statement of Interest

K.N.F. has received grants and served as consultant, advisor, or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire, and others.

E.V. has received grants and served as consultant, advisor, or CME speaker for the following entities: Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lilly, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

A.H.Y. is employed by King's College London, is Honorary Consultant SLAM (NHS UK), has paid lectures by and participated in advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders, and no shareholdings in pharmaceutical companies. He was lead investigator for Embolden Study (AZ), BCI Neuroplasticity Study, and Aripiprazole Mania Study; investigator initiated studies from AZ, Eli Lilly, Lundbeck, and Wyeth; and has received grant funding (past and present) from NIHR-BRC (UK); NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK).

H.G. within the last 3 years received grant/research support from NIHR UK, MRC UK, and NTW NHS Foundation Trust; received honoraria or consultation fees from Gedeon-Richter, Lundbeck, and Hofmann-LaRoche; and participated in a company-sponsored speaker's bureau for BMS, Ferrer, Janssen-Cilag, Otsuka, Lundbeck, and Pfizer.

L.Y. has been on speaker/advisory boards for, or has received research grants from Alkermes, Allergan, AstraZeneca, Bristol Myers Squibb, CANMAT, CIHR, Eli Lilly, Forest, GlaxoSmithKline, Intas, Janssen, the Michael Smith Foundation for Health Research, Pfizer, Servier, Sumitomo Dainippon, Sunovion, and the Stanley Foundation.

S.K. within the last 3 years received grants/research support, consulting fees, and honoraria from Angelini, AOP Orphan



Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier.

H.J.M. received honoraria for lectures or for advisory activities or received grants by the following pharmaceutical companies: Lundbeck, Servier, Schwabe, and Bayer. He was president or on the executive board of the following organizations: CINP, ECNP, WFSBP, and EPA and chairman of the WPA section on pharmacopsychiatry.

P.B. has received research grants, honoraria for participation in advisory boards, and/or gave presentations from Allergan, Astra Zeneca, Bristol Myers Squibb, Canadian Institute for Health Research, Eli Lilly, Lundbeck, Janssen, Ontario Brain Institute, Meda-Valeant, Merck, Otsuka, Pierre Fabre Medicaments, Pfizer, Shire, Sunovion, and Takeda.

## References

- Akiskal HS, Walker P, Puzantian VR, King D, Rosenthal TL, Dranon M (1983) Bipolar outcome in the course of depressive illness. Phenomenologic, familial, and pharmacologic predictors. *J Affect Disord* 5:115–128.
- Appleby L (1991) Suicide during pregnancy and in the first postnatal year. *BMJ* 302:137–140.
- Arnold LM, McElroy SL, Keck PE Jr (2000) The role of gender in mixed mania. *Compr Psychiatry* 41:83–87.
- Badger TA, McNiece C, Bonham E, Jacobson J, Gelenberg AJ (2003) Health outcomes for people with serious mental illness: a case study. *Perspect Psychiatr Care* 39:23–32.
- Bauer MS (2002) A review of quantitative studies of adherence to mental health clinical practice guidelines. *Har Rev Psychiatry* 10:138–153.
- Bauer MS, Kirk GF, Gavin C, Williford WO (2001a) Determinants of functional outcome and healthcare costs in bipolar disorder: a high-intensity follow-up study. *J Affect Disord* 65:231–241.
- Bauer MS, Mitchner L (2004) What is a “mood stabilizer”? An evidence-based response. *Am J Psychiatry* 161:3–18.
- Bauer MS, Williford WO, Dawson EE, Akiskal HS, Altshuler L, Fye C, Gelenberg A, Glick H, Kinoshian B, Sajatovic M (2001b) Principles of effectiveness trials and their implementation in VA Cooperative Study #430: ‘Reducing the efficacy-effectiveness gap in bipolar disorder’. *J Affect Disord* 67:61–78.
- Berk L, Jorm AF, Kelly CM, Dodd S, Berk M (2011) Development of guidelines for caregivers of people with bipolar disorder: a Delphi expert consensus study. *Bipolar Disord* 13:556–570.
- Blehar MC, DePaulo JR Jr, Gershon ES, Reich T, Simpson SG, Nurnberger JI Jr (1998) Women with bipolar disorder: findings from the NIMH Genetics Initiative sample. *Psychopharmacol Bull* 34:239–243.
- Bonnin CM, Reinares M, Hidalgo-Mazzei D, Undurraga J, Mur M, Saez C, Nieto E, Vazquez GH, Balanza-Martinez V, Tabares-Seisdedos R, Vieta E (2015) Predictors of functional outcome after a manic episode. *J Affect Disord* 182:121–125.
- Brockington IF, Cernik KF, Schofield EM, Downing AR, Francis AF, Keelan C (1981) Puerperal psychosis. Phenomena and diagnosis. *Arch Gen Psychiatry* 38:829–833.
- Calabrese JR, Fava M, Garibaldi G, Grunze H, Krystal AD, Laughren T, Macfadden W, Marin R, Nierenberg AA, Tohen M (2014) Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. *J Affect Disord* 168:439–451.
- Charney DS, et al. (2003) Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry* 60:664–672.
- Chengappa KR, Goodwin GM (2005) Characterizing barriers, challenges and unmet needs in the management of bipolar disorder. *Bipolar Disord* 7:5–7.
- Chengappa KR, Williams P (2005) Barriers to the effective management of bipolar disorder: a survey of psychiatrists based in the UK and USA. *Bipolar Disord* 7:38–42.
- Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML (1994) A reevaluation of risk of in utero exposure to lithium. *JAMA* 271:146–150.
- Coverdale JH, Turbott SH (2000) Sexual and physical abuse of chronically ill psychiatric outpatients compared with a matched sample of medical outpatients. *J Nerv Ment Dis* 188:440–445.
- Coverdale JH, Turbott SH, Roberts H (1997) Family planning needs and STD risk behaviours of female psychiatric out-patients. *Br J Psychiatry* 171:69–72.
- Curtis V (2005) Women are not the same as men: specific clinical issues for female patients with bipolar disorder. *Bipolar Disord* 7:16–24.
- Davidson J, Robertson E (1985) A follow-up study of post partum illness, 1946–1978. *Acta Psychiatr Scand* 71:451–457.
- Dunner DL, Patrick V, Fieve RR (1979) Life events at the onset of bipolar affective illness. *Am J Psychiatry* 136:508–511.
- Fakhoury WK, Wright D, Wallace M (2001) Prevalence and extent of distress of adverse effects of antipsychotics among callers to a United Kingdom National Mental Health Helpline. *Int Clin Psychopharmacol* 16:153–162.
- Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, Keck PE Jr (2002) The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry* 63:284–287.
- Frye MA, Altshuler LL, McElroy SL, Suppes T, Keck PE, Denicoff K, Nolen WA, Kupka R, Leverich GS, Pollio C, Grunze H, Walden J, Post RM (2003) Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. *Am J Psychiatry* 160:883–889.
- Frye MA, Gitlin MJ, Altshuler LL (2004) Unmet needs in bipolar depression. *Depress Anxiety* 19:199–208.
- Frye MA, Prieto ML, Bobo WV, Kung S, Veldic M, Alarcon RD, Moore KM, Choi DS, Biernacka JM, Tye SJ (2014) Current landscape, unmet needs, and future directions for treatment of bipolar depression. *J Affect Disord* 169:17–23.
- Gerson LD, Rose LE (2012) Needs of persons with serious mental illness following discharge from inpatient treatment: patient and family views. *Arch Psychiatr Nurs* 26:261–271.
- Glauser TA, Cerenzia W, Wiley S, Howson A, Thase M (2013) Identifying psychiatrists’ practice patterns when managing depression in patients with bipolar I disorder: a descriptive study to inform education needs. *Postgrad Med* 125:144–153.
- Goossens PJ, Knoppert-van der Klein EA, Kroon H, van Achterberg T (2007) Self-reported care needs of outpatients with a bipolar disorder in the Netherlands. *J Psychiatr Ment Health Nurs* 14:549–557.
- Grande I, Berk M, Birmaher B, Vieta E (2016) Bipolar disorder. *Lancet* 387:1561–1572.
- Grof P, Robbins W, Alda M, Berghoefer A, Vojtechovsky M, Nilsson A, Robertson C (2000) Protective effect of pregnancy in women with lithium-responsive bipolar disorder. *J Affect Disord* 61:31–39.
- Han C, Wang SM, Lee SJ, Patkar AA, Masand PS, Pae CU (2013) Dilemma for enhancing psychiatrists’ adherence to guideline (evidence)-based practice. *Expert Rev Neurother* 13:751–754.



- Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C (2000) Gender and bipolar illness. *J Clin Psychiatry* 61:393–396; quiz 397.
- Hirschfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 64:161–174.
- Hyun M, Friedman SD, Dunner DL (2000) Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar disorder* 2:131–135.
- Johnson RE, McFarland BH (1996) Lithium use and discontinuation in a health maintenance organization. *Am J Psychiatry* 153:993–1000.
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59:530–537.
- Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 60:261–269.
- Keck PE Jr, McElroy SL, Strakowski SM, Stanton SP, Kizer DL, Balistreri TM, Bennett JA, Tugrul KC, West SA (1996) Factors associated with pharmacologic noncompliance in patients with mania. *J Clin Psychiatry* 57:292–297.
- Kendell RE, Chalmers JC, Platz C (1987) Epidemiology of puerperal psychoses. *Br J Psychiatry* 150:662–673.
- Ketter TA (2010) Nosology, diagnostic challenges, and unmet needs in managing bipolar disorder. *J Clin Psychiatry* 71:e27.
- Leibenluft E (1996) Women with bipolar illness: clinical and research issues. *Am J Psychiatry* 153:163–173.
- Leibenluft E (2000) Women and bipolar disorder: an update. *Bull Menninger Clin* 64:5–17.
- Lewis L (2000) The national depressive and manic-depressive association: an introduction. *Biol Psychiatry* 47:692.
- Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM (1994) The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord* 31:281–294.
- Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, Sachs G (2014) Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 171:160–168.
- Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Hartwell N, Iqbal MI (1997) Lower risk of suicide during pregnancy. *Am J Psychiatry* 154:122–123.
- Masand PS, Tracy N (2014) Results from an online survey of patient and caregiver perspectives on unmet needs in the treatment of bipolar disorder. The primary care companion for CNS disorders 16.
- McElroy SL (2014) Pros and cons of approved therapies for bipolar depression and ongoing unmet needs. *J Clin Psychiatry* 75:e26.
- McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI, Faedda GL, Swann AC (1992) Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry* 149:1633–1644.
- McElroy SL, Frye MA, Suppes T, Dhavale D, Keck PE Jr, Leverich GS, Altshuler L, Denicoff KD, Nolen WA, Kupka R, Grunze H, Walden J, Post RM (2002) Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry* 63:207–213.
- McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, Konarski JZ, Kennedy SH (2007) Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. *Curr Opin Psychiatry* 20:406–416.
- Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 68:241–251.
- Morgan VA, Mitchell PB, Jablensky AV (2005) The epidemiology of bipolar disorder: sociodemographic, disability and service utilization data from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Bipolar disorder* 7:326–337.
- Morselli PL, Elgie R, Europe G (2003) GAMIAN-Europe/BEAM survey I—global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. *Bipolar disorder* 5:265–278.
- Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F (2013) Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. *J Affect Disord* 151:1003–1008.
- Nivoli AM, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, Bonnin CM, Grande I, Sanchez-Moreno J, Vieta E, Colom F (2011) Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. *J Affect Disord* 133:443–449.
- Ogilvie AD, Morant N, Goodwin GM (2005) The burden on informal caregivers of people with bipolar disorder. *Bipolar disorder* 7:25–32.
- Packer S (1992) Family planning for women with bipolar disorder. *Hosp Community Psychiatry* 43:479–482.
- Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE, Jr., McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA (2003) Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry* 64:680–690; quiz 738–689.
- Reinares M, Vieta E, Colom F, Martinez-Aran A, Torrent C, Comes M, Goikolea JM, Benabarre A, Daban C, Sanchez-Moreno J (2006) What really matters to bipolar patients' caregivers: sources of family burden. *J Affect Disord* 94:157–163.
- Russell JM, Mackell JA (2001) Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. *CNS drugs* 15:537–551.
- Sachs GS (2003) Unmet clinical needs in bipolar disorder. *J Clin Psychopharmacol* 23:S2–8.
- Sachs GS (2013) Unmet needs in the assessment and management of bipolar I depression. *J Clin Psychiatry* 74:e11.
- Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, Nierenberg AA, Fava M, Bowden C, Ketter T, Marangell L, Calabrese J, Kupfer D, Rosenbaum JF (2003) Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 53:1028–1042.
- Schopf J, Rust B (1994) Follow-up and family study of postpartum psychoses. Part I: overview. *Eur Arch Psychiatry Clin Neurosci* 244:101–111.
- Sharma V, Persad E (1995) Effect of pregnancy on three patients with bipolar disorder. *Ann Clin Psychiatry* 7:39–42.
- Siddiqui O, Hung HM, O'Neill R (2009) MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat* 19:227–246.

- Simon GE, Ludman E, Unutzer J, Bauer MS (2002) Design and implementation of a randomized trial evaluating systematic care for bipolar disorder. *Bipolar Disord* 4:226–236.
- Smith S, Wheeler MJ, Murray R, O'Keane V (2002) The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. *J Clin Psychopharmacol* 22:109–114.
- Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, Carson WH, Marcus RN, Owen R (2008) Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol* 28:13–20.
- Vieta E (2014) Antidepressants in bipolar I disorder: never as monotherapy. *Am J Psychiatry* 171:1023–1026.
- Vieta E, Cruz N (2012) Head to head comparisons as an alternative to placebo-controlled trials. *Eur Neuropsychopharmacol* 22:800–803.
- Weissman MM, Prusoff BA, Merikangas KR (1984) Is delusional depression related to bipolar disorder? *Am J Psychiatry* 141:892–893.
- Wells KB (1999) Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. *Am J Psychiatry* 156:5–10.
- Wells KB, Miranda J, Bauer MS, Bruce ML, Durham M, Escobar J, Ford D, Gonzalez J, Hoagwood K, Horwitz SM, Lawson W, Lewis L, McGuire T, Pincus H, Scheffler R, Smith WA, Unutzer J (2002) Overcoming barriers to reducing the burden of affective disorders. *Biol Psychiatry* 52:655–675.
- Wieck A, Haddad PM (2003) Antipsychotic-induced hyperprolactinaemia in women: pathophysiology, severity and consequences. Selective literature review. *Br J Psychiatry* 182:199–204.